REMARKS/ARGUMENTS

The present application was filed on February 7, 2002, with 67 claims: method claims 1-41 and composition claims 42-67. The claims as filed were canceled and replaced with formulation claims 68-91 in an accompanying Preliminary Amendment.

In the Office Action under reply, the claims stand rejected as follows:

1. claims 68-87 as nonenabling under 35 U.S.C. § 112, first paragraph;
2. claims 68-91 as obvious under 35 U.S.C. § 103(a) over Carson et al.; and
3. claims 68-91 as obvious under 35 U.S.C. § 103(a) over Ashida.

These rejections are addressed in part by the claim amendments presented with this paper and are otherwise traversed for the reasons set forth in the discussions relating to each rejection.

THE CLAIM AMENDMENTS:

With the present amendment, claim 68 has been amended to delete the term "preventing" and to add a list of skin conditions that may be treated with the claimed pharmaceutical composition. Claim 88 has also been amended to clarify the use of the claimed pharmaceutical formulation for use in treating skin conditions, disorders, and diseases associated with inflammation, and to add a list of skin conditions that may be treated with the claimed pharmaceutical formulation, i.e., allergic contact dermatitis, atopic dermatitis, actinic keratosis, keratinization disorders, epidermolysis bullosa diseases, exfoliative dermatitis, seborrheic dermatitis, erythemas, discoid lupus erythematosus, dermatomysositis, and skin cancer.

Claim 92 has been added to the application to further define the chemopreventive properties of the claimed pharmaceutical formulation. Support for the subject matter of new claim 92 is found in the specification at page 19, lines 1-3, and Example 7. Accordingly, no new matter has been added to the application with the addition of claim 92.

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 68-87 stand rejected under 35 U.S.C. § 112, first paragraph as not enabling. The Examiner contends that the claims, while enabling for treating skin conditions, diseases, and disorders associated with inflammation, are not enabling for preventing skin conditions, diseases, and disorders associated with inflammation.

While applicants do not agree with the Examiner's position, for the sake of expediting the prosecution of this application, applicants have amended independent claim 68 to delete the term

"preventing" from the scope of the claim. With this amendment, the rejection of claims 68-87 as non-enabling is rendered moot. Accordingly, applicants respectfully request reconsideration and withdrawal of this rejection.

THE REJECTION UNDER 35 U.S.C. § 103(A) OVER CARSON ET AL.

Claims 68-91 stand rejected under 35 U.S.C. § 103(a) as obvious over Carson et al. (U.S. Patent No. 6,270,780 filed July 27, 1997). This rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, three criteria must be met: first, the prior art reference must teach or suggest the claimed combination; second, the Office must show that the ordinary artisan would be motivated to modify the reference or to combine the reference teachings; and third, there must be a showing that the ordinary artisan would have a reasonable expectation of success at arriving at the claimed combination based *solely* on the teachings of the cited prior art reference. *In re Rouffet,* 149 F.3d 1350, 1357 (Fed. Cir. 1998); *In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991).

As recited in claim 68, the present invention relates to a topical pharmaceutical formulation for use in preventing or treating skin conditions, disorders and diseases associated with inflammation, comprising a topical carrier and a therapeutically effective concentration of an active agent selected from the group consisting of resveratrol, pharmacologically acceptable salts, esters, amides, prodrugs and analogs thereof, and combinations of any of the foregoing, wherein the skin condition, disorder, or disease is selected from the group consisting of allergic contact dermatitis, atopic dermatitis, actinic keratosis, keratinization disorders, epidermolysis bullosa diseases, exfoliative dermatitis, seborrheic dermatitis, erythemas, discoid lupus erythematosus, dermatomysositis, and skin cancer.

The disclosure of Carson et al. is premised on the finding that resveratrol is a phytoestrogen (col. 2, lines 44-45). Carson et al. explains that phytoestrogens are natural compounds that have estrogen-like activity and which are found in plants (col. 2, lines 12-15). Carson et al. notes that estrogens have been found to increase the thickness of the dermal layer and reduce wrinkle formation in aging facial skin (col. 1, lines 49-52). Accordingly, the premise of Carson et al. is that resveratrol, as a phytoestrogen, may be used as a replacement for estrogen therapy. Accordingly, the premise of Carson et al. is that resveratrol may be used to: (i) deliver estrogenic activity to the skin; (ii) inhibit keratinocyte proliferation in human skin; and (iii) increase keratinocyte differentiation (col. 3, lines 45-48; Examples 2, 3, and 4). In describing other uses of resveratrol, Carson et al. notes that resveratrol has been shown to be a potent cancer chemopreventive agent as well as an anti-inflammatory agent (col. 2, lines 62-66).

With respect to the chemopreventive properties of resveratrol, Carson et al. does ***not*** elaborate on this aspect of resveratrol and certainly neither teaches or suggests that resveratrol may be topically

applied to the skin to inhibit cellular events associated with tumor initiation, promotion, and progression (claim 92).

With respect to resveratrol's anti-inflammatory properties, at Example 6, Carson et al. notes that resveratrol is a cyclo-oxygenase (COX) inhibitor and that COX inhibitors are believed to be anti-inflammatory agents because they reduce the conversion of arachidonic acid to pro-inflammatory substances, such as prostaglandins (col. 12, lines 34-37). Carson et al., however, does not set forth ***any*** inflammatory diseases or disorders may be treated with resveratrol. On this matter, it must be noted that when Carson et al. discusses the use of resveratrol to treat psoriasis or winter xerosis, the resveratrol is suggested as a treatment for these diseases on the basis of its use an agent to treat ***skin hyperproliferation disorders*** and ***not*** on the basis of its use as an anti-inflammatory agent.

Against this background, Carson et al. teaches the use of resveratrol for topical application to mammalian skin that is dry, flaky, lined, wrinkled, aged, photodamaged, or to healthy skin for prophylactic purposes (col. 3, lines 37-41). Carson et al. also provides that the resveratrol may be used for treatment of skin proliferation disorders such as psoriasis or winter xerosis (col. 3, lines 42-44). In addition, Carson et al. teaches that resveratrol is useful for cosmetic lightening of skin color and to control skin irritation, sting, or inflammation caused by alpha-hydroxy acids (col. 3, lines 49-54; Examples 5, 6 and 7). As indicated by the single claim of Carson et al., the preferred embodiment of the invention, and the only one claimed, is a composition that includes a combination of resveratrol and hydroxy acid (col. 4, lines 51-52; claim 1). The purpose of including resveratrol with the hydroxy acid in one formulation is to reduce the irritation, sting, or inflammation often associated with the use of hydroxy acids (col. 3, lines 49-52). As explained at col. 5, an advantage of combining resveratrol with the alpha hydroxy acids is that higher amounts of hydroxy acids may be used without causing skin irritation (col. 5, lines 16-18). Further, as explained in Example 6, it is not the anti-inflammatory properties of resveratrol that make the addition of resveratrol to alpha hydroxy formulations useful, rather, it is the ability of resveratrol to reduce ***irritation*** caused by alpha hydroxy acids (col. 12, liens 37-42).

Carson et al. does not establish a *prima facie* case of obviousness for the following reasons.

First, it is self-evident that Carson et al. fails to teach the use of resveratrol to treat the recited inflammatory skin disorders. While Carson et al. mentions that resveratrol has anti-inflammatory properties, Carson et al. does ***not*** suggest that resveratrol may be used to treat inflammatory skin disorders, such as those of the claimed invention, for the following reasons: (i) Carson et al. does ***not*** mention whether the anti-inflammatory properties of resveratrol are directed to external or internal inflammation; and (ii) Carson et al. does ***not*** mention whether the anti-inflammatory properties of resveratrol are derived from an oral or topical administration of the agent.

Second, although Carson et al. mentions that resveratrol may be used to treat psoriasis and winter xerosis, Carson et al. mentions this use of resveratrol within the context of resveratrol being useful to treat *skin hyperproliferation disorders, **not** inflammatory skin disorders*. Accordingly, based upon this teaching alone, the ordinary artisan would be motivated to modify Carson et al. to apply topical resveratrol to other skin hyerproliferation disorders, but ***not*** the inflammatory skin disorders of the claimed invention.

Third, even with the disclosure that resveratrol has been shown to have anti-inflammatory properties, the ordinary artisan faced only with this broad sweeping teaching would not have a reasonable expectation of success at arriving at the claimed invention without undue experimentation. Because Carson et al. is concerned with aging skin, photodamaged skin, and skin irritated from cosmetic preparation, one of ordinary skill in the art would have to deviate very far from the teachings of Carson et al. to arrive on the path pursued by the present inventors.

Because claims 68-91 are not rendered obvious by Carson et al., applicants respectfully request reconsideration and withdrawal of this rejection.

THE REJECTION UNDER 35 U.S.C. § 103(A) OVER ASHIDA

Claims 68-91 stand rejected under 35 U.S.C. § 103(a) as obvious over Ashida (JP 4093288410 A filed December 22, 1997).

Ashida teaches 0.001 to 5 wt.% of resveratrol in a cosmetic preparation containing yucca extract, saponin, and flavone. Ashida explains that the cosmetic is produced by chipping at least one of the roots or stems of the yucca and optionally drying it prior to crushing it into a powder. The yucca powder is then soaked in an ethanol-water mixed solvent to prepare the yucca extract, which is formulated into a cosmetic. The ethanol-water mixed solvent contains 75 to 95 wt.% of ethanol. The cosmetic preparation of Ashida is taught only for antimicrobial, ultraviolet absorption, and skin conditions such as rough skin and malting.

Ashida is even further removed from the claimed invention than Carson et al. Ashida neither teaches nor suggests that the resveratrol-ethanol formulation has any anti-inflammatory abilities; accordingly, one of ordinary skill in the art would have no motivation to apply the resveratrol-ethanol formulation to any inflammatory condition. Further, even if the ordinary artisan, by mere serendipity, applied the Ashida resveratrol-ethanol formulation to inflamed skin, he or she would have no reasonable expectation that the formulation would have an effect on the inflamed skin; any noticeable effect would be a stroke of good fortune and not one derived from reading Ashida.

Because claims 68-91 are not rendered obvious by Ashida, applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

The foregoing amendments and remarks address and resolve each of the outstanding rejections in this application. Accordingly, applicants respectfully request entry of the foregoing claim amendments, withdrawal of all outstanding rejections, and passage of this application to allowance.

If the Examiner has any questions regarding this Amendment or the application in general, he is invited to contact the undersigned by phone at 650-330-4913 or by e-mail at canaan@reedpatent.com.

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